DTI in Amyotrophic Lateral Sclerosis.

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UPPER AND LOWER MOTOR NEURONS INVOLVED

- Upper motor neuron: Slow movement, spasticity
- Lower motor neuron: Weakness, fasciculations
- Functional abnormality is primarily related to loss of lower motor neurons
- ALSFRS-R is key functional scale

PYRAMIDAL CELLS AND CST

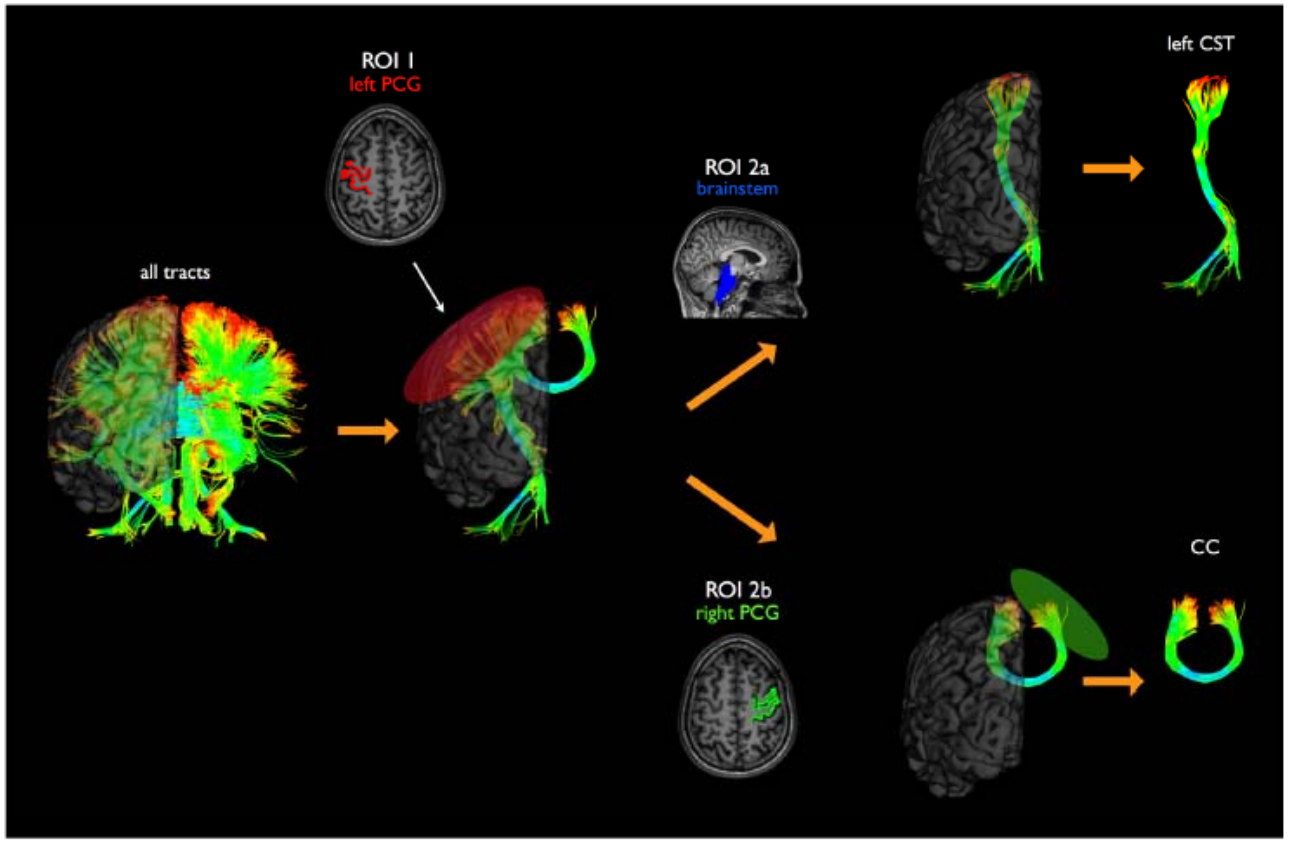

Figure 5. Selection of corticospinal tract (CST) and corpus callosum (CC) fibers. First, all fibres were tracked. Secondly, the left precentral gyrus was selected as region of interest (ROI 1) and the fibres touching this ROI were selected. Thirdly, the brainstem was selected as second ROI (ROI 2a). The left CST was defined by all fibres touching both ROI 1 and ROI 2a. Finally, a third ROI (ROI 2b) was defined as the right precentral gyrus. The CC was defined by all fibres touching both ROI 1 and ROI 2b. The tracts of the right CST were defined in a similar manner. ROI = region of interest. PCG = precentral gyrus. CST = corticospinal tract. CC = corpus callosum.
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REGIONAL DISORDER

- Bulbar, Arm, Limb Involvement
  - Represented in different regions of cortex
  - May start and remain in one region for years
  - Onset and current site of involvement
- Cognitive Involvement
  - Classic FTD (5% of cases)
  - Subtle “cognitive-apathetic” syndrome

SPINAL CORD

- SPINAL CORD
  - Brunt of disease in many cases
  - Direction of degeneration unclear
- Involvement may never reach cortex

Practical Concerns

- ORTHOPNEA
  - One third will die within a year of entering research trial
  - About half of patients will not be able to lie flat due to respiratory difficulty from weakness in diaphragm and throat
- COMFORT, TRAVEL and TRANSFERS

Case Study: Spinal

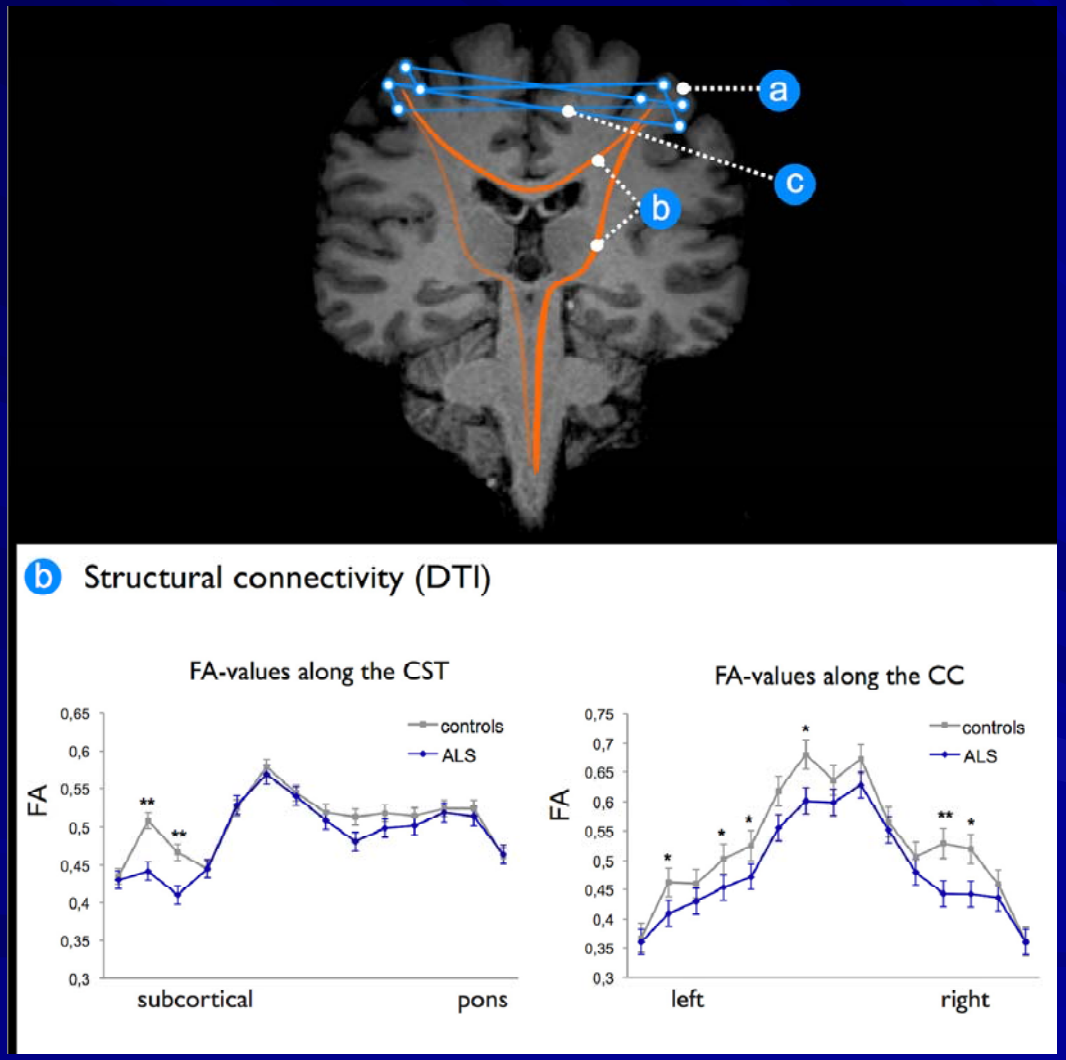
- 1999: Right foot drop
- 2001: Diagnosis, legs weak, brisk knee reflexes
- 2002: Difficulty standing up, arms weak, respiratory difficulty
- Late 2002: Died of respiratory failure
- Autopsy: Cortex is normal
  - Involvement of spinal gray and white matter (worst in thoracic regions)

Case Study: Cortical

- 2005: Right foot drop
  - Upper motor neuron signs in arms and legs
- 2006: Atrophy in hands, slurred speech
  - Apathy, mild cognitive impairment
- 2007: Died of bulbar and respiratory failure
- Autopsy: Marked loss of neurons in motor cortex and pallor in CST

Cross Sectional DTI Studies

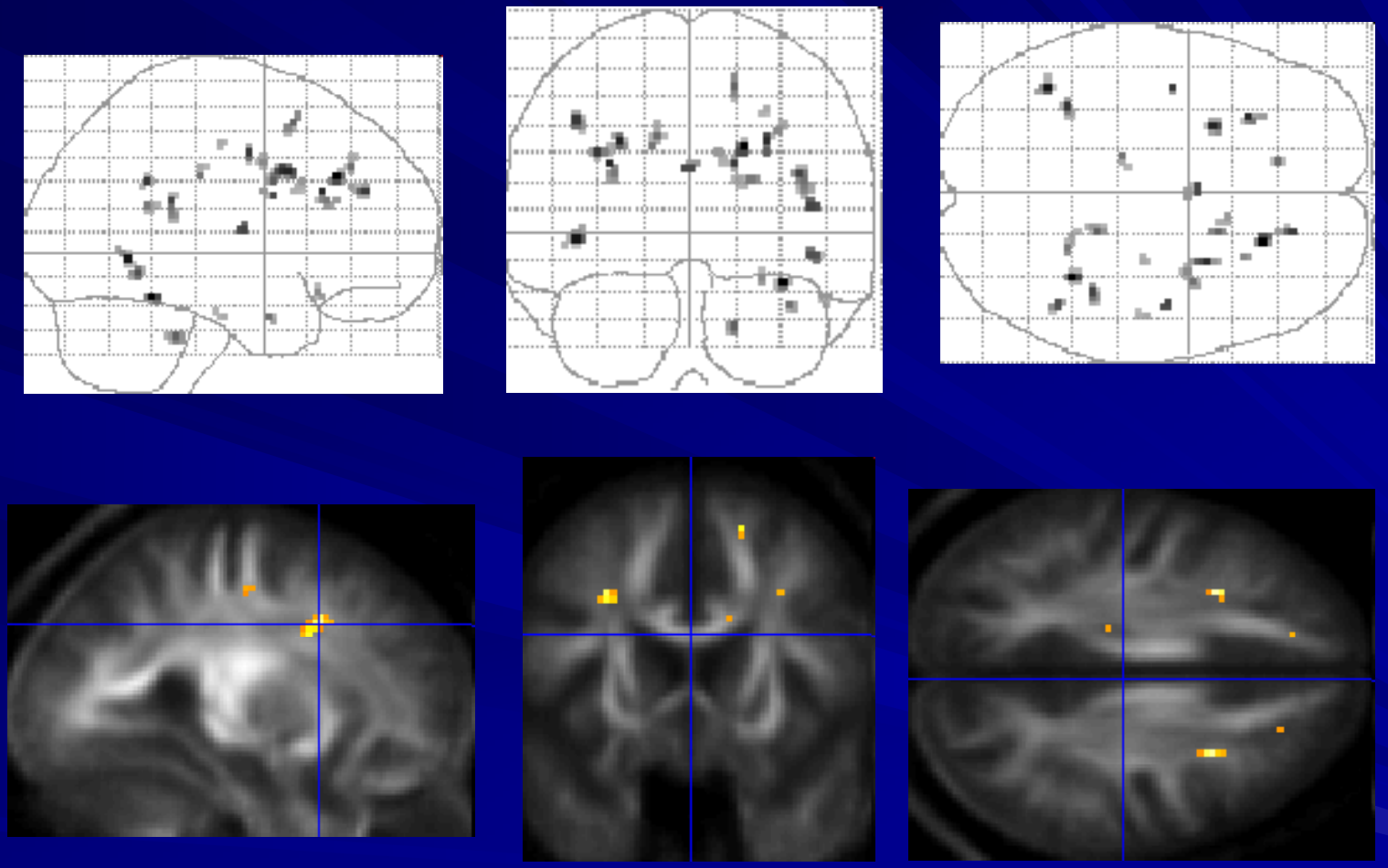
- ALS compared to controls
  - Reduced FA in CST
- Correlational studies
  - Decreased CST FA correlates with severity of motor signs or length of disease
- Correlational studies with upper motor neuron signs
  - More inconsistent


a
b
c
b Structural connectivity (DTI)
FA-values along the CST
FA
0,65
0,6
0,55
0,5
0,45
0,4
0,35
0,3
controls
ALS
**
**
subcortical
pons
FA-values along the CC
FA
0,75
0,7
0,65
0,6
0,55
0,5
0,45
0,4
0,35
0,3
controls
ALS
*
*
*
*
**
*
left
right

Correlation: DTI and Apathy

- 24 cognitively normal patients with ALS
- Look for correlation with self and caregiver reports of apathy
- Look for MRI signs of early frontal lobe change
- No obvious DTI differences (outside of CST) between patients and matched controls

Patient Self Ratings
Symptoms of Apathy Correlated with ↓ FA



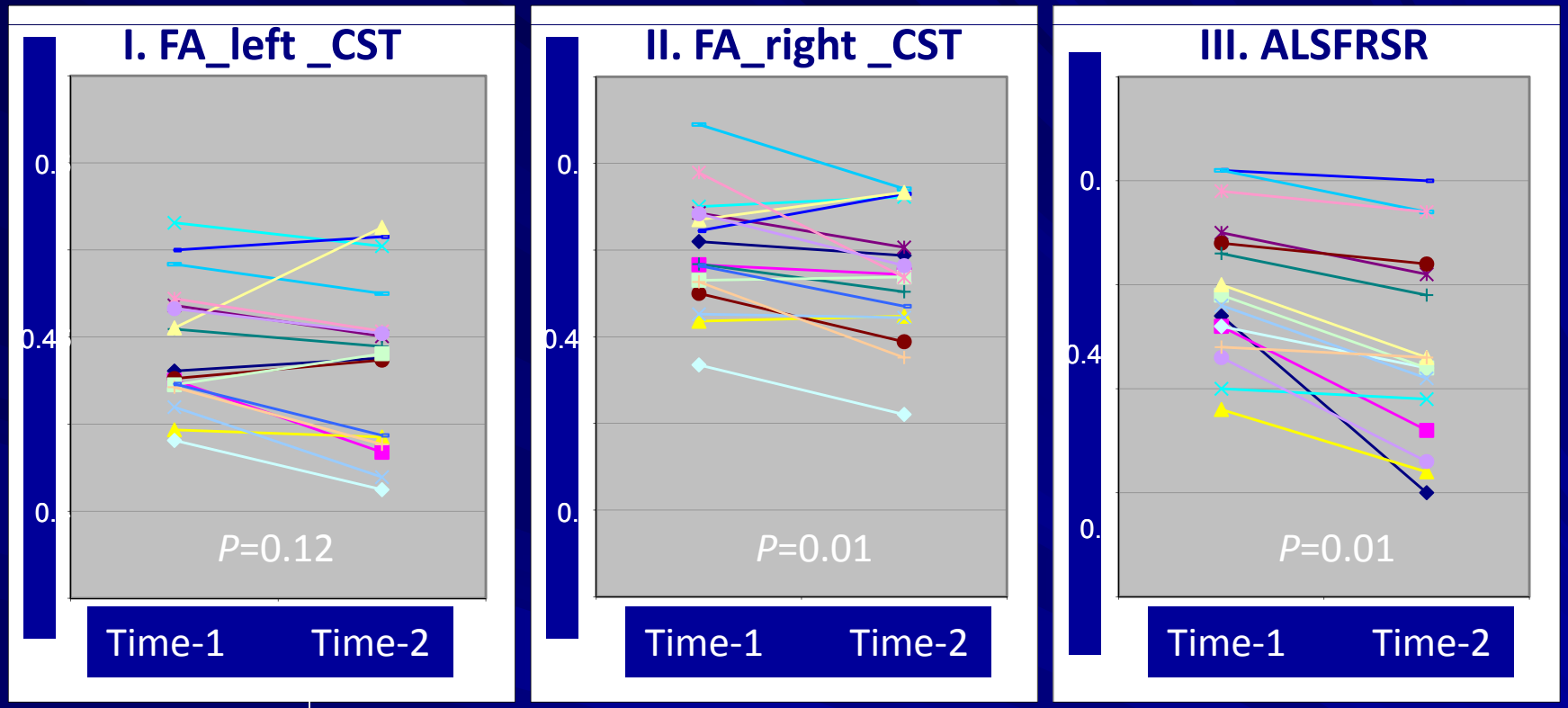
Longitudinal DTI Studies

FA changes (n=16)

		FA_{CST}-1 M(SD)	FA_{CST}-2 M(SD)	ΔFA M(SD)	Change Rate* (/yr)
Left	Ctrl.	0.5562 (0.01)	0.5571 (0.01)	0.0006 (0.016)	0.30% (5.83)
	ALS	0.5260 (0.03)	0.5245 (0.04)	-0.0015 (0.011)	-0.67% (4.24)
Right	Ctrl.	0.6005 (0.03)	0.5945 (0.03)	-0.0063 (0.007)	-2.08% (2.38)
	ALS	0.5650 (0.04)	0.5539 (0.04)	-0.016 (0.022)	-3.92% (7.71)

* Change Rate = (FA1 – FA2) / FA1 × 100 × 2

Longitudinal DTI in Amyotrophic Lateral Sclerosis

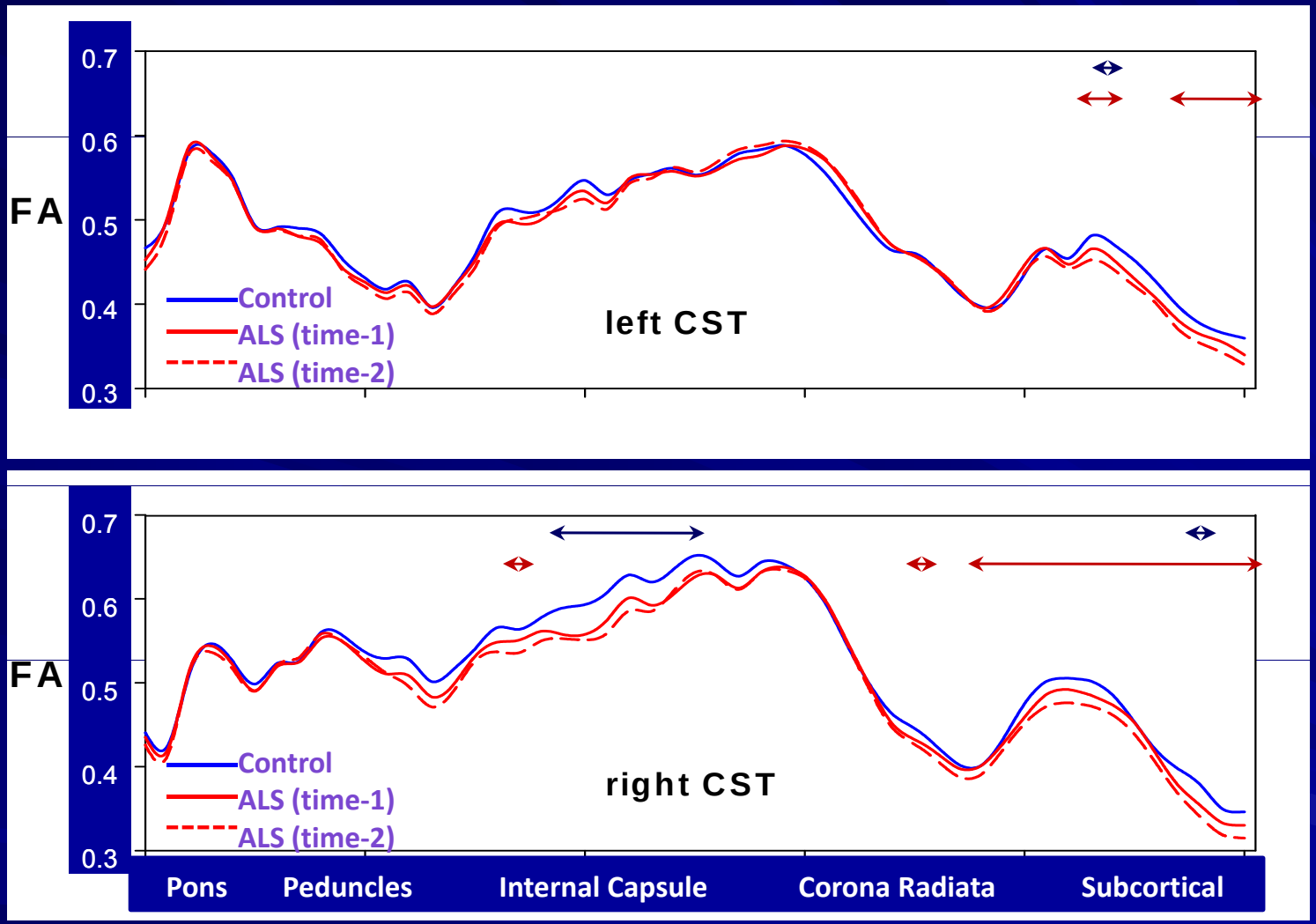


Measurements	Time-1	Time-2	Annual Change Rate	*P* value*
FA_left_CST	0.448 ± 0.02	0.443 ± 0.02	-1.97 ± 4.9 %	0.12
FA_right_CST	0.475 ± 0.02	0.467 ± 0.02	-2.66 ± 3.7 %	0.01
ALSFRSR	34.63 ± 7.1	29.19 ± 9.3	-25.6 ± 19 %	0.01

* Paired- samples t-test

DTI in Amyotrophic Lateral Sclerosis

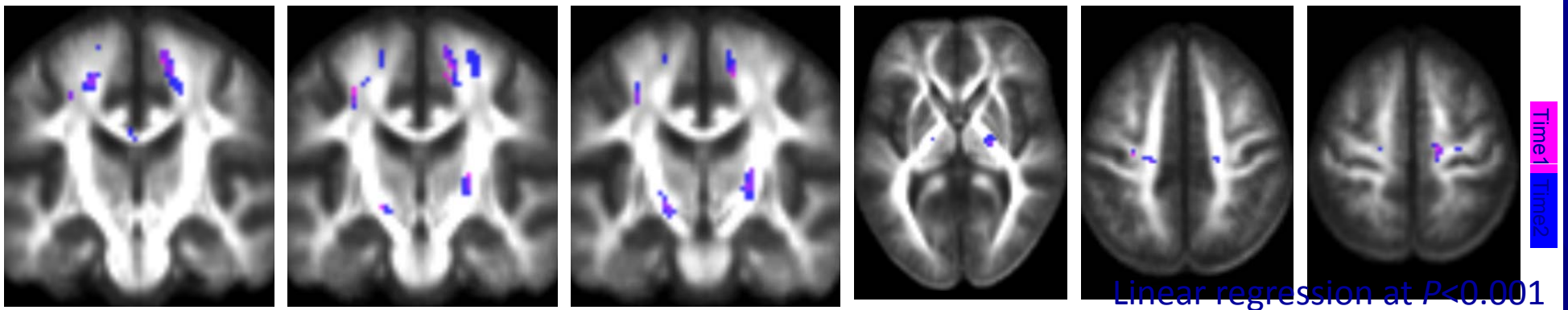
Group Mean FA along CST by slices



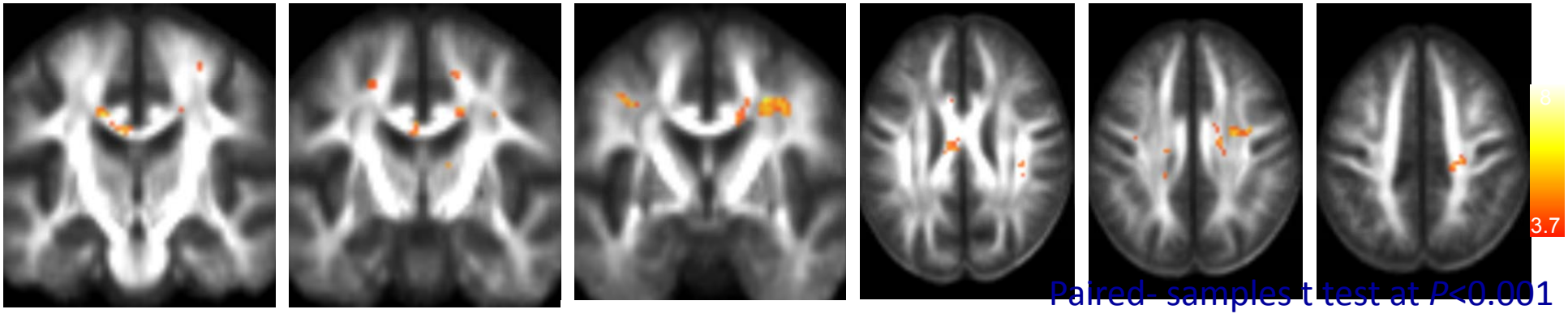
Longitudinal DTI in Amyotrophic Lateral Sclerosis

Differences in ALS vs. Control and ALS time-1 vs. ALS time-2

I. Overlay: ALS (time-1) < Control ALS (time-2) < Control



II. ALS (time-2) < ALS (time-1)

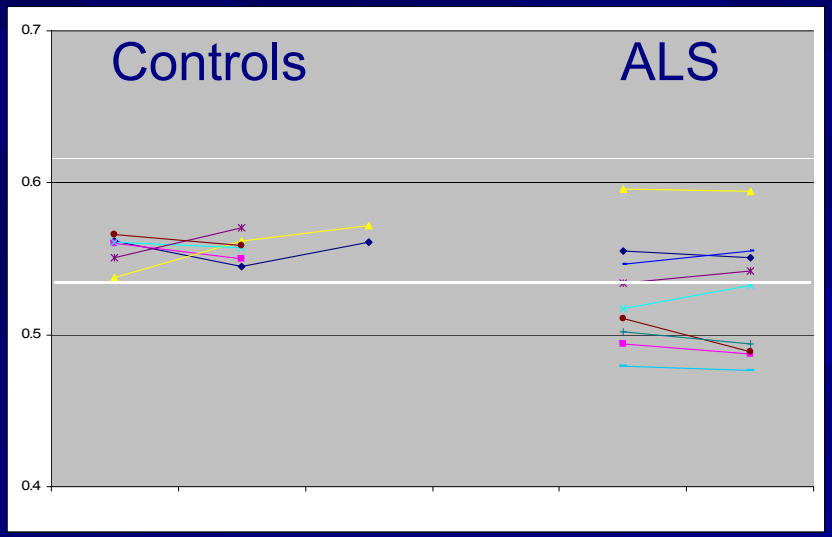


Diagnostic Studies

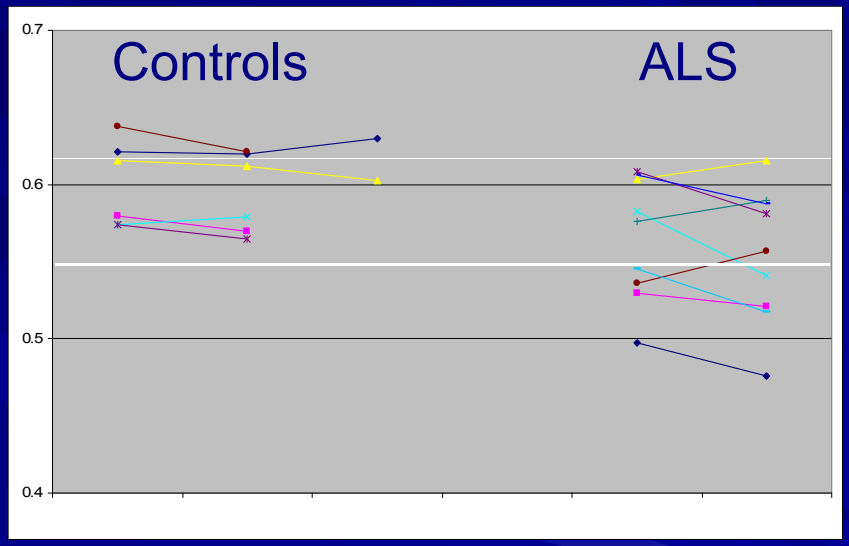
- About half of ALS patients have abnormal FA measures at baseline
  - Overlap with controls
- Role for spinal cord imaging
- Clinical correlation to manage expectations
  - Cognitive involvement
  - Bulbar involvement

DTI-Corticospinal tract ALS

Right



Left



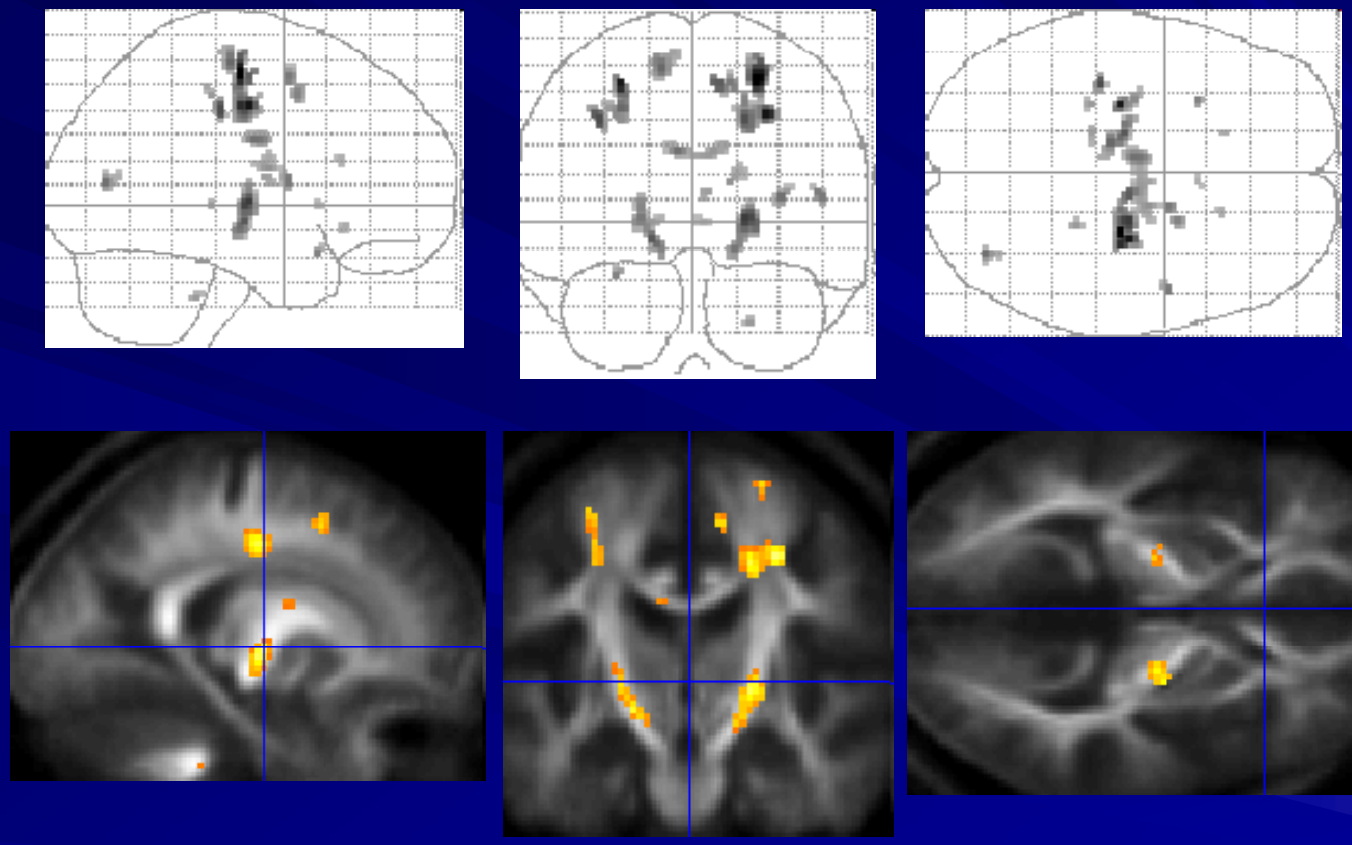
Study

- Categorization scheme using two basic phenotypes
- **Generalized ALS** (G-ALS): Upper motor neuron involvement in the bulbar region
- **Localized ALS** (L-ALS): Upper motor neuron involvement limited to the limbs at the time of the study

Results

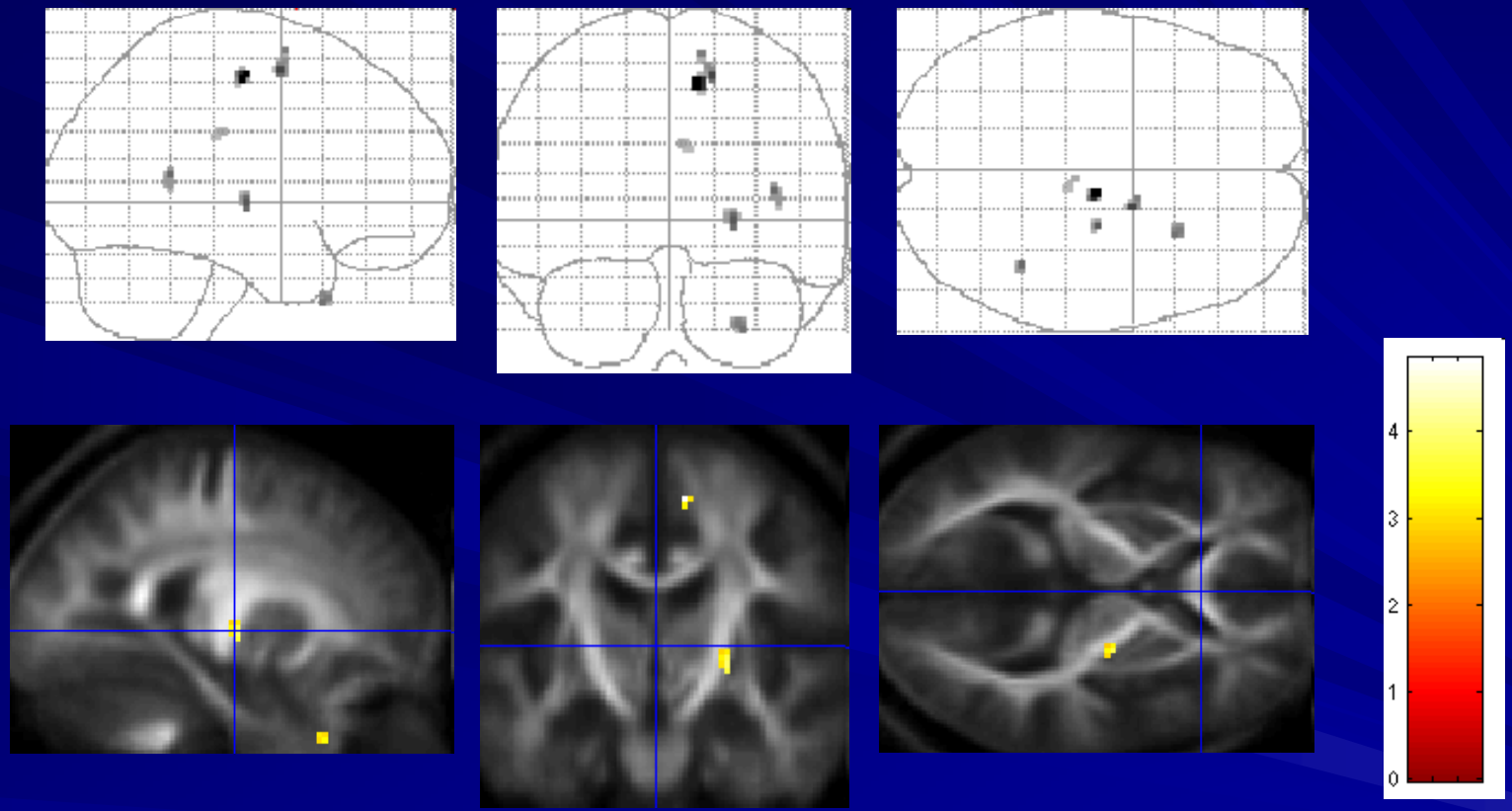
	GALS	LALS
N	5	11
Duration	17.5	32.8
FVC	82.5	98.2
ALSFRS-R	33	37

Baseline: FA reduction in GALS vs. Controls



T-value

Baseline FA reduction in LALS vs. Controls



T-value

Right side motor fibers

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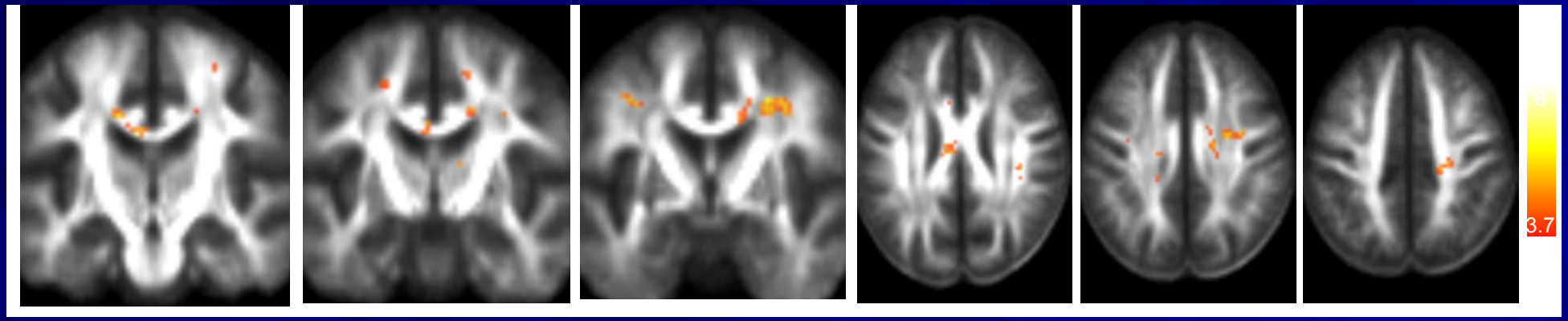
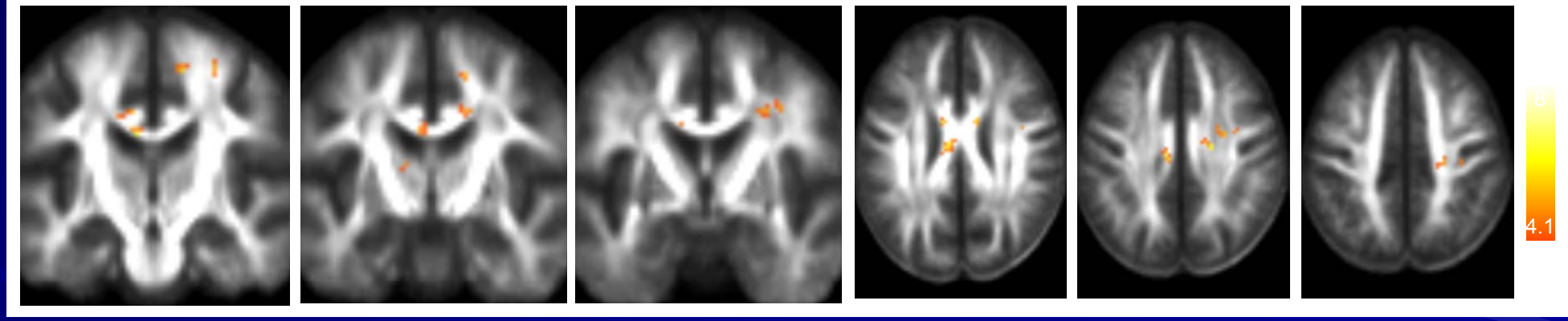
Differences in ALS time-1 vs. ALS time-2

Paired- samples t test at $P<0.001$



Localized ALS (time-2) < Localized ALS (time-1)



Generalized ALS No significant differences

Predicting Outcomes